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2013 CHS Executive Committee

President                Dr. Aaron Schimmer
Past-President           Dr. Tom Nevill
Vice-President           Dr. Lynne Savoie
Secretary Treasurer      Dr. Molly Warner
Executive Vice-President Dr. Gail Rock

Editor: Microenvironment Dr. Tom Nevill

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Support of trainees and junior faculty, remains a top priority

The past presidents of the Canadian Hematology Society (CHS) include many Canadian hematology giants and I am privileged and humbled to follow in their footsteps as I assume the presidency of the CHS. First, I would like to thank our out-going president, Dr. Stephen Couban, for his hard work and contributions to the CHS. Under Stephen’s leadership, the CHS has embarked on a number of new and exciting initiatives including re-establishing a Canadian hematology meeting that will occur in June 2014 and initiating a bid to host the 2018 meeting of the International Hematology Society (ISH) in Vancouver. I look forward to working with Stephen to bring these events to fruition.

I would also like to extend a warm welcome to Dr. Lynne Savoie who is our in-coming Vice President. I am grateful that Dr. Molly Warner continues to serve as our treasurer and secretary and Dr. Tom Nevill continues as the editor of the Microenvironment newsletter.

Dr. Gail Rock remains a linchpin in the Society in her role as Executive Vice President. I am thankful for the all of time and effort our executive members devote to the CHS. We are also fortunate to have Jean and Lisa in our CHS head office. Along with Dr. Rock, they are the glue that holds the Society together and keeps us moving forward.

Over the next several months, the CHS will make a formal bid to host the 2018 ISH meeting in Vancouver. The bid process is being spearheaded by Drs. Nevill and Rock and early feedback from the ISH selection committee is encouraging. Hosting ISH will be a significant honor and provide an opportunity to highlight the great hematology research being conducted in this country.

Canada will also be hosting other major international hematology meetings in the next few years. For example, the International Society for Hematology and Stem Cells will be held in Montreal in August of 2014 and the International Society for Thrombosis and Hemostasis.
will take place in Toronto in 2015.

Canadian hematologists are leading the organization of these meetings. In this issue of the Microenvironment, you can read more about these conferences and the roles of our CHS members in organizing these meetings. If you are organizing similar meetings of potential interest to Canadian hematologists, you are encouraged to send us notices.

Supporting research by hematology trainees and junior faculty remains a priority of the CHS. We continue to provide research awards related to abstracts presented at ASH. In addition, we offer small research grants in the form of the R.K. Smiley awards.

With grant funding becoming ever tighter, we hope this funding will support exciting and important Canadian hematology research.

In the 2014 competition, we received 25 applications spanning the breadth of hematology, including benign, malignant, and laboratory hematology.

We received applications related to clinical, translational and fundamental hematology research. The review of these applications is underway and the award recipients will be featured in the next edition of the newsletter.

Over the next two years, we will also embark on new initiatives to promote Canadian hematology research and details will be forthcoming in the future editions of the Microenvironment.

In February, I had the opportunity to represent the CHS at the National Employment Summit organized by the Royal College Physicians and Surgeons of Canada.

This meeting addressed issues of physician human resources and physician underemployment with the long-term goal of optimally aligning physician resources to ensure an adequate supply and distribution of physicians to meet the needs of our country in a fiscally responsible manner.

It became clear through this meeting that achieving this goal will require an understanding of the current and future needs of physician resources in Canada. It was also evident that the national specialty societies, such as the CHS, will have a critical role to play in this process.

For example, I think the CHS can play a leading role in collecting and communicating available hematology practice opportunities in the country. Identifying open hematology positions in Canada, is an important step to determine hematology resources and needs in the country.

These data, along with population trends and projections, will help address the question of how many hematologists do we need and where are they needed. Over the next few months, we will begin the process to collect this information.

We will be asking you to help identify open hematology practice opportunities in your community and hospital. Your response is critical for our new hematology colleagues who are starting their careers.

I hear frequently about the anxiety among current and prospective hematology trainees who are concerned about career opportunities upon completion of training. By helping us identify and communicate open hematology positions, you will be offering tremendous assistance to our new hematology colleagues.

In addition, highlighting open hematology positions and fellowship opportunities will also help recruit the best and brightest medical students and internal medicine residents to our field.

In closing, I would like to thank you for your continued commitment to the CHS and the hematology community in Canada.

Your membership dues sustain the educational and research activities of the Society and allow CHS to be a hub for hematology in the country. For those who may not be members yet, I would encourage you to visit our website (www.canadianhematologysociety.org) and learn more about the benefits of membership.

However, membership dues alone do not cover the full operating costs, and we are very grateful for our Gold, Silver and Bronze industry partners.

You will see their logos and names in the Microenvironment. When you meet the representatives of these companies, I ask you to thank them for their support of the CHS.
Dear Colleagues,

As announced at the CHS Reception at ASH, many of you will know that the CHS and the Canadian Blood and Marrow Transplant Group (CBMTG) are hosting a combined symposium in Halifax on Friday June 13, 2014. I sincerely hope you will consider attending!

Years ago until 1999, Canadian hematologists gathered together in Canada during the Royal College meeting to present data and discuss issues of relevance. Then, for eight years the CHS very successfully organized an annual symposium in conjunction with a previous CBMTG or other subspecialty groups.

This year, after an eight year hiatus, I am very pleased to announce that we are again planning a Canadian hematology meeting in Canada. In addition to the CBMTG and CHS, a number of other Canadian hematology groups are meeting in Halifax on June 13, 2014 including the Canadian Apheresis Group (CAG), VECTOR (a group of hematologists with interest in research in thrombosis) and the CNTRP (a research group of clinicians and scientists from the solid organ and BMT fields).

At both the CHS and CBMTG, we welcome you to this meeting and hope that that this meeting will become a new Canadian tradition!

Please join us and have the members of your teams, including your trainees join us as well!

Stephen Couban, Chair
Scientific Organizing Committee

Welcome! CHS meets in June 2014 in Halifax

Friday June 13, 2014
9:00 am to 3:45 pm
The Westin Nova Scotian—Halifax, NS

PROGRAM

8:45—9:00 am Welcome
9:00—10:00 am Dr. Neal Young
The Diagnosis and Treatment of Severe Aplastic Anemia
10:00—11:00 am Dr. Sudeep Shivakumar & Dr. Marc Carrier
Thrombosis Challenges in Patients with Hematologic Malignancies
11 am—noon Dr. Danièle Marceau
Paroxysmal Nocturnal Hemoglobinuria
2:30 pm—3:15 pm Dr. Paul Moorehead
Hemophilia treatment: “In the Clinic and in the Future”
3:15 pm—3:45 pm Dr. Eiad Kahwash
Single Unit Transfusion

Message du Président

L’appui pour la recherche des stagiaires en hématologie et la faculté junior, reste une haute priorité

Les anciens présidents de la Société canadienne d’hématologie (SCH) inclus plusieurs géants d’hématologie et je suis privilégié et humble de suivre dans leurs pas en assumant la présidence de la SCH. Premièrement, j’aimerais remercier notre président départant, Dr. Stephen Couban, pour son travail et ses contributions à la SCH.

Sous la dirigeance de Stephen, la SCH s’est embarquée sur un nombre d’initiatives nouvelles et excitants incluant le rétablissement de la rencontre annuelle d’hématologie qui va avoir lieu en Juin 2014 ainsi que l’initiation d’une proposition pour accueillir la rencontre de la Société internationale d’hématologie à Vancouver en 2018. J’espère travailler avec Stephen pour continuer le progrès sur ces événements.

J’aimerais aussi faire un accueil chaleureux à Dr. Lynne Savoie qui est maintenant notre nouvelle vice-présidente. Je suis reconnaissant que Dr. Molly Warner continue de servir comme trésorière et secrétaire et Dr. Tom Nevill qui continue comme éditeur de la publication Microenvironnement.

Dr. Gail Rock continue comme pivot dans la société dans son rôle de vice-présidente exécutive. Je suis reconnaissant pour tout le temps et l’effort que nos membres exécutifs dévouent à la SCH. De plus, nous sommes chanceux d’avoir Jean et Lisa au bureau de la SCH. Travailant avec Dr. Rock, elles gardent la société ensemble et aident à continuer le cheminement en avant.

Pendant les prochains mois, la SCH va soumettre une proposition formelle pour accueillir la rencontre de la Société internationale d’hématologie (SIH) à Vancouver, en 2018. Dr. Nevill et Dr. Rock sont en tête du processus de soumission et la rétroaction du comité de sélection est encourageante. Accueillir la SIH sera un grand honneur et va fournir une opportunité de surligner la recherche formidable qui se déroule dans ce pays.


Vous pouvez en lire plus sur ces conférences, ainsi que sur le rôle que nos membres de la SCH ont dans leur organisation, dans cette publication du Microenvironnement. Si vous organisez des rencontres semblables, d’intérêt potentiel aux hématologues Canadiens, vous êtes encouragés de nous contacter.

L’appui pour la recherche des stagiaires en hématologie et la faculté junior, reste une haute priorité pour la Société canadienne d’hématologie.

Nous continuons de fournir des prix de recherches reliés aux sommets présentés à ASH. De plus, nous offrons des petites bourses de recherches R. K. Smiley. Avec des bourses de recherches de plus en plus difficile à obtenir, nous espérons que ces bourses fourniront des recherches importantes dans le domaine d’hématologie au Canada. Dans la compétition en 2014, nous avons reçu 25 applications étendue largement dans l’hématologie, incluant l’hématologie, bénin, malin et laboratoire. Nous avons reçu des applications reliées à la recherche hémato-oncologique clinique, translatique et fondamentale. La revue de ces applications est en marche et les lauréats seront inclus dans la prochaine édition de la publication. Pendant les prochains 2 ans, nous allons aussi embarquer sur des nouvelles initiatives pour promouvoir la recherche hémato-oncologique Canadienne et plus de détails se-
A 23-year-old woman presented with a 2-week history progressive abdominal and lower extremity swelling with associated fatigue and an 8 kg weight loss.

- A CBC showed a hemoglobin of 62 g/L, a WBC of 16.5 x 10⁹/L and platelets of 70 x 10⁹/L.
- Chemistry revealed: potassium of 3.2 mmol/L, normal serum creatinine of 95 umol/L, uric acid 450 umol/L (upper normal 360), alkaline phosphatase of 643 U/L (upper normal 125), GGT 400 U/L (upper normal 65), total/direct bilirubin of 84/60 umol/L and an LDH of 260 U/L (upper normal 240).
- CT scan showed extensive lymphadenopathy in the neck, axillae, mediastinum, mesentry and pelvis as well as hepatosplenomegaly, marked ascites and peritoneal seeding.
- Peripheral blood and bone marrow examinations are shown in Figures 1 and 2, respectively. **Do you know the diagnosis?**

*Page 4*

En février, j’ai eu l’occasion de représenter la SCH au Sommet national sur l’emploi des médecins organisé par le Collège royal des médecins et chirurgiens du Canada.

Cette rencontre a adressé la question des ressources humaines et sous-emploi de médecins et avait comme but d’aligner, à long terme, les ressources de médecins pour s’assurer une provision adéquate et la distribution de médecins pour rencontrer les besoins de notre pays avec une bonne responsabilité fiscale.

C’est devenu clair à la rencontre qu’obtenir ce but va nécessiter une compréhension des besoins immédiats et futurs des ressources de médecins au Canada. C’était aussi évident pendant cette rencontre que les sociétés spéciales nationales, tel que la SCH, va avoir un rôle important à jouer dans ce processus. Par exemple, je crois que la SCH peut jouer un rôle principal à collectionner et communiquer des opportunités d’emplois en hématologie dans le pays.

Un pas important pour déterminer les ressources et besoins hématologiques dans le pays est d’identifier des positions ouvertes de positions en hématologie. Ces données, ainsi que des statistiques de population et des projections, vont aider à adresser la question de combien d’hématologistes que l’on a besoin et où on en a de besoin.

Vos cotisations soutiennent les activités éducatives et de recherche de la société et permet à la SCH d’être le pivot pour l’hématologie au Canada. Pour conclure, j’aimerais vous remercier pour votre support continu de la SCH et la communauté d’hématologie au Canada.

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Leukemic engraftment in NOD.SCID mice is correlated with clinical parameters and predicts outcome in human AML

- Dr. James Kennedy
- University of Toronto
- Supervisor: Dr. Jean Wang

NOD.SCID xenotransplantation assays are a powerful tool for studying the biology of acute myeloid leukemia (AML).

The investigators transplanted peripheral blood or bone marrow cells from 307 AML patients into sublethally irradiated NOD.SCID mice and were able to achieve myeloid engraftment in 134 cases (44%). This included 40% of samples taken at AML diagnosis and 66% of samples taken at AML relapse although only 2 patients failed to generate a graft at diagnosis but did generate a graft at relapse.

Engraftment was associated with a higher WBC count (p=0.01) but, most striking was the correlation of engraftment with cytogenetic risk group.

Xenografts were generated in only 4/30 patients (13%) with favourable karyotypes, 63/153 patients (41%) with intermediate-risk karyotype and 23/43 patients (53%) with adverse karyotypes (p=0.002). Furthermore, in normal karyotype AML patients, FLT3-ITD-positive patients established xenografts in 50% of samples compared to 27% of FLT3-ITD-negative cases (p=0.04).

Clinical outcome was shown to be closely correlated with ability to generate xenografts with only ~50% of patients entering complete remission if their samples produced engraftment compared with 80% of patients with non-engrafting samples (p <0.0001). This resulted in a difference in both event-free and overall survival between the two groups (p <0.0001).

The authors have convincingly demonstrated that the ability to engraft NOD.SCID mice with cells from an AML patient does correlate with clinical outcome. However, further work is needed to provide insight into the underlying determinants of this engraftment ability and to clarify if the engraftment behaviour is truly an independent prognostic indicator in AML. -ed.
Normal range of bleeding scores for the ISTH-BAT: adult and pediatric data from the merging project

- Dr. Malak Elbatarny
- Queens University, Kingston, ON
- Supervisor: Dr. Paula James

Standarized quantitative bleeding assessment tools (BATs) are utilized to report hemorrhagic symptoms and the International Society on Thrombosis and Hemostasis (ISTH) assessment tool (ISTH-BAT) was introduced in 2010 to consolidate and optimize previously described BATs, including the Vicenza Bleeding Questionaire. However, the normal ranges of the ISTH-BAT have not been determined and this study sought to establish the normal range for this tool in both adult and pediatric patients.

The investigators compiled bleeding score data from different studies that utilized Vicenza-based BATs using a specifically created bioinformatics system. The proposed normal ranges were then determined by removing outliers (> 3 standard deviations from the mean) and then selecting the mid-95th percentile.

The authors analyzed demographic and bleeding score data on 1079 adult (mean age 43 years) and 343 pediatric (mean age 9 years) subjects.

Normal ranges for the ISTH-BAT were established as 0-4 in adults and 0-2 for children less than age 18 years of age.

This study definitively established normal ranges for the ISTH-BAT, a critical step in objectively assessing bleeding symptoms. This should aid researchers in investigating the correlation between bleeding symptoms and genotypic, molecular and environmental data.

Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma

- David Twa, MSc
- British Columbia Cancer Agency, Vancouver, BC
- Supervisor: Dr. Christian Steidl

Primary mediastinal large B-cell lymphoma (PMBCL) is an aggressive malignancy typically seen in young woman. Analysis of genomes and transcriptomes have highlighted inactivating mutations of TP53, amplification of chromosome 9p and chromosomal translocations involving CIITA as being linked to the pathogenesis of PMBCL.

The researchers decided to explore the link between two programmed death ligands located at 9p24.1, PDL1 and PDL2, and PMBCL. They performed break-apart FISH analysis on 551 clinical samples [125 PMBCL patients, 134 nodal diffuse large cell lymphoma patients (DLBCL), 130 primary CNS DLBCL patients, 82 testicular DLBCL and 80 other lymphoma patients] and 20 established cell lines. FISH analysis revealed that 20% of the PMBCL samples were positive for one of the two PDL genes, significantly more than in any other lymphoma (p <0.05). This compared with 1% in CNS DLBCL, 3% in nodal DLBCL and 7% in testicular DLBCL; none of the other lymphomas were positive for a PDL FISH abnormality.

Further analysis revealed PDL locus amplification in 45/125 (36%) of PMBCL samples.

Following analysis of whole genome and whole RNA transcriptome libraries, the authors were able to characterize four novel fusion transcripts involving 9p24.1 locus found in one clinical case and three PMBCL cell lines.

This interesting study suggests that rearrangements involving the PDL locus are recurrent and relatively unique to PMBCL, leading to overexpression of PDL transcripts. This may well provide a therapeutic avenue to explore in this particular malignancy.
Determining cell-of-origin subtypes in diffuse large B-cell lymphoma using gene expression profiling on formalin-fixed paraffin-embedded tissue – an L.L.M.P.P. project

- Dr. David Scott
- British Columbia Cancer Agency, Vancouver, BC
- Supervisor: Dr. Randy Gascoyne

The cell-of-origin (COO) can separate diffuse large B-cell lymphoma (DLBCL) into germinal centre B cell (GCB) and activated B cell (ABC) subtypes based upon molecular characteristics.

With new therapeutic agents being developed with selective activity against GCB and ABC DLBCL, this study sought to create a robust and accurate molecular gene expression profile (GEP) assay (using a NanoString technology 20 gene assay) that could be applied to formalin-fixed paraffin-embedded tissue (FFPET). The investigators examined 119 cases of DLBCL (51 in a training cohort and 68 in a validation cohort) that had previously had COO assigned by gold-standard frozen-GEP analysis; all but 3 samples provided gene expression data of sufficient quality. COO was assigned in parallel at two different sites, the BCCA in Vancouver, BC and the NCI in Frederick, Maryland and showed 98% concordance.

The COO for all gold-standard GCB cases was 100% concordant when tested with NanoString on FFPET. ABC DLBCL samples were correctly assigned in 93% of cases using the same NanoString technology.

This study demonstrates that accurate and rapid classification of COO is possible for DLBCL cases at diagnosis using routinely obtained FFPET. The value of this testing will depend upon the development of COO-specific therapy in DLBCL.

Epidemiology of post-transplant lymphoproliferative disorders following solid organ transplantation in a major Canadian transplant centre

- Dr. Anthea Peters
- University of Alberta, Edmonton, AB

Post-transplant lymphoproliferative disorder (PTLD) can be a serious early or late complication in patients that undergo solid organ transplantation (SOT).

This project involved the review of over 4500 patients that underwent SOT between 1984 and 2011 and identified 133 cases of PTLD.

The PTLD cohort included 61 cases that were classified as “early” (< 2 years after SOT), 31 cases as “late” (2-7 years after SOT) and 39 cases as “very late” (> 7 years after SOT).

The cumulative incidence of PTLD was 2.6% at 5 years, 4.3% at 10 years and 7.9% at 20 years. Patients aged 0-5 years had the highest risk of early PTLD, perhaps because there was an increased risk of early PTLD in EBV-negative recipients receiving organs from EBV-positive donors.

Furthermore, the highest risk of early PTLD was in patients transplanted between 1984 and 1991 and the lowest risk in patients transplanted in the last decade of the study.

Multivisceral SOT and lung transplantation conferred the highest risk of PTLD, particularly late PTLD, and kidney transplant recipients had the lowest risk of any PTLD.

This study provides an excellent retrospective overview of PTLD in the SOT setting. The cumulative incidence of PTLD is significant following SOT although it is decreasing with time and is dependent upon recipient age, EBV serostatus and organ transplanted. -ed.
History Corner

Robert L. Noble and E. Clark Noble

Noble brothers legacy a major contribution to hematology

Robert L. Noble and E. Clark Noble were brothers born into a prominent medical family, Robert (b. February 3, 1910), 10 years junior to Clark (b. December 29, 1900).

Their father, Robert T. Noble, was a GP who served as president of the Ontario Medical Association, the Canadian Medical Association, the College of Physicians and Surgeons of Ontario and the Medical Council of Canada. Clark Noble entered University of Toronto in 1918, majoring in physiology and biochemistry. He would go on to medical school and graduated with honours in 1925.

A brush with fame

However, he had his first brush with fame that began with his undergraduate classmate and best friend, Charles Best, and both were talented semi-pro baseball players.

Clark Noble and Charles Best began work as summer students in J. J. R. MacLeod’s laboratory in 1921 and were joined by a young surgeon, Frederick Banting. It was decided (by a coin toss!) that Best would assist Banting for the first month and Noble for the second.

In an experiment that Macleod was skeptical about in the first place, Banting and Best performed canine pancreactectomies, made extracts, injected them into diabetic dogs and measured blood glucose levels.

Dr. J.B. Collip was brought in to help purify the extracts but left in a dispute with Banting. Clark Noble’s month of assistance never came to be and Best was subsequently put in charge of insulin production in Toronto. Nevertheless, Clark Noble’s laboratory efforts contributed to the rapid increase in knowledge about insulin while Noble himself continued to work on it and its already to go, if anyone is interested... commercial supply of fish insulin never came to pass.

In October 1923, Banting and, somewhat ironically, J. J. R. MacLeod were awarded the Nobel Prize for the discovery of insulin.

Clark Noble went on to spend the summer of 1923 evaluating the feasibility of using fish as a commercial source of insulin.

He did extensive work in the cod fish industry but ultimately, evidence began to accumulate that large-scale production of fish insulin was impractical.

Charles Best and Clark Noble disagreed on this point and, not surprisingly, the former had a long and distinguished career in medical research while the latter became a GP in Toronto.

Major contribution to hematology

It was as a result of his ongoing interest in diabetes that led to Clark and his brother Robert to make a major contribution in the field of hematology.

In 1952, a patient of Clark Noble’s visited Jamaica and collected 25 leaves from the Madagascar periwinkle plant (Vinca rosea), which was commonly made into a tea to treat patients with diabetes, and sent it to him in an envelope. Clark was no longer involved in research and had no facilities to test the leaves for medicinal value so, he sent the envelope to his brother, Robert.

Robert L. Noble graduated from University of Toronto Medical School in 1934 before pursuing a PhD at the University of London in England.

In another twist of irony, he returned to Canada in 1937 and began to work with Dr. J. B. Collip who, by now, was studying endocrine-related cancers at McGill University.

In 1947, he became the Associate Director of the Collip Medical Research Institute at the University of Western Ontario.

With the arrival of the envelope of leaves sent by his brother Clark, Robert began studying the effects of the leaf extracts on blood glucose levels.

It turned out that the leaf extracts had little effect on glucose levels but did have inhibitory effects on white blood cells and the bone marrow.

Vinblastine isolated and purified

In 1954, Charles T. Beer, an organic chemist, joined Robert Noble’s research team and together they isolated and purified a potent alkaloid extract in 1958 that they called “Vinblastine”.

The team worked with Eli Lilly Co. to develop a small supply of Vinblastine for clinical trials, with the first occurring at Princess Margaret Hospital in Toronto in 1959.

Vinblastine and a related vinca alkaloid, Vincristine, both went on to become mainstays of chemotherapy in a number of different cancers, especially lymphoblastic leukemia and lymphoma.

In honour of this ground-breaking discovery, The National Cancer Institute of Canada subsequently named its most prestigious award for excellence in research the Robert L. Noble Prize.

Robert L. Noble became the Director of Cancer Research and Professor of Physiology at the University of British Columbia in 1960. He was a skilled experimentalist and his research generated more than 200 publications.

He retired in 1975 but continued his research as an honorary member of the Division of Cancer Endocrinology at the BC Cancer Agency until his death on December 11, 1990. In 1997, Dr. Robert L. Noble was inducted into The Canadian Medical Hall of Fame along with Dr. Charles Beer.

Dr. E. Clark Noble continued his interest in fish insulin and was interviewed by the Toronto Star in 1974 during an impending insulin shortage. Despite his assurances, “...we’ve done all the work on it and its already to go, if anyone is interested...”, commercial supply of fish insulin never came to pass.

Dr. E. Clark Noble died on May 18, 1978 and while there was no mention of his passing in the CMAJ at the time, an article did appear on his life and brushes with fame in December 2002.1

A 32-year-old woman is referred with a mild, non-progressive pancytopenia first identified at age 14 when she presented with idiopathic lymphedema of the left lower extremity.

She had three bone marrow examinations over the subsequent two decades which showed increasingly prominent trilineage dysplasia but no increase in blast cells and a normal female karyotype.

She reports a several year history of severe warts on her hands and feet as well as frequent respiratory tract infections.

Current blood work reveals a mild neutropenia an absolute lymphopenia and monocytopenia.

An association between myeloid malignancy and idiopathic lymphedema was first observed by Emberger in 1979, although a pathogenetic link was initially elusive. Not surprisingly, progress in molecular genetics has led to a better understanding of the connection between these two uncommon disorders.

The GATA gene family is a group of six zinc finger-containing transcription factors found in multiple tissues. GATA1, GATA2 and GATA3 are primarily expressed in hematopoietic tissue and are lineage specific; GATA1 is expressed in erythroid cells, eosinophils and megakaryocytes and GATA3 is expressed in T-cells. GATA1 has been linked to hematologic disease and mutations of this gene are seen in acute megakaryocytic leukemia and the transient myeloproliferation seen in Down syndrome.

GATA2 (short for GATA-2 binding protein) is expressed in hematopoietic stem cells and myeloid progenitors and plays a critical role in their differentiation as well as in the regulation of tissue and alveolar macrophages. Murine experiments show that GATA2 mutations, when homozygous, are fatal during gestation and, when heterozygous, induce stem cell apoptosis thereby reducing absolute stem cell numbers.

The GATA2 gene is located at 3q21.3 and its protein product consists of two DNA-binding zinc finger domains (ZF) and four flanking sequences [two transactivation domains (TAD), a nuclear localization signal (NLS) and a negative regulatory domain (NRD)] (Figure 1).

GATA2 mutations were first shown to play a role in hematologic disease in a CML patient with blast phase transformation.

The key breakthrough in the linking of GATA2 mutations to hematologic disorders was an abstract presented at the American Society of Hematology Annual Meeting in 2010. This paper described four families with autosomal dominant MDS/AML that were shown to have mutations in the second zinc finger of the GATA2 gene. This report followed on a publication earlier that year from the National Institutes of Health in Bethesda, MD describing a novel condition, MonoMAC syndrome, an autosomal dominant and sporadic monocyte/macrophage dysfunction with a predisposition to mycobacterial infections.

Researchers at the NIH, who were searching for a causative gene, were intrigued by the Scott abstract and began examining their patient cohort for GATA2 mutations. They quickly identified that all of those affected with MonoMAC syndrome had N-terminal mutations around the two zinc fingers leading to premature termination of GATA2 gene translation.

As this exciting new work was unfolding in North America, the UK Lymphedema Consortium was making progress of their own in understanding the link between MDS and lymphedema by describing 7 new cases of autosomal dominant AML with lymphedema (‘Emberger syndrome’). These cases had some common and interesting features – close set eyes, epicanthic folds, web neck, long tapering fingers, precocious MDS, recurrent cellulitis in the affected limb and generalized warts. Concurrent with the discovery of GATA2 mutations as underlying MonoMAC syndrome was a publication from the Consortium clearly linking the MDS/lymphedema disorder with similar GATA2 mutations.

The publication of these two seminal papers in September 2011 led to a better understanding of the spectrum of diseases that can be linked to GATA2 mutations, shown diagrammatically in Figure 2. It is now clear that GATA2 mutations may manifest as recurrent non-TB mycobacterial/fungal infections (due to the monocytopenia) associated with sinopulmonary bacterial infections/avgeolar proteinosis (due to alveolar/tissue macrophage dysfunction) – the MonoMAC phenotype. However, these same identical mutations may produce Emberger syndrome (lymphedema, cellulitis and panniculitis), dendritic cell-monocyte-B/NK lymphoid (“DCML”) deficiency syndrome (papillomavirus and EBV infections with associated anogenital malignancies), familial MDS/AML (without any other associated manifestations), all with considerable potential for overlap, and even an apparently normal phenotype. The common hematologic link for...
A 58-year-old man presents with a 3 month history of fatigue, night sweats and left upper quadrant pain. He has a history of having had a myocardial infarction 5 years previously at which point he was found to have hypertension and hypercholesterolemia.

His CBC shows a Hemoglobin of 102 g/L, WBC of 156 x 10^e9/L with a left shift including 2% blasts and a platelet count of 769 x 10^e9/L.

Physical examination reveals a spleen that is 8 cm below the left costal margin.

Bone marrow examination shows 100% cellularity with eosinophilia, 9% basophils and 3% blast cells.

Cytogenetics reveal t(9;22) in all 50 metaphases analyzed.

How should this patient be managed?

CML is a rare disease with an incidence of 1-2 cases per 100,000 people per year. It is characterized by the obligatory presence of a reciprocal chromosomal translocation t(9;22)(q34;11) that leads to fusion of the ABL gene from chromosome 9 and the BCR gene from chromosome 22. The resulting Philadelphia chromosome (Ph) produces the BCR-ABL1 fusion protein with dysregulated tyrosine kinase activity mediating the leukemic phenotype.

The diagnosis of CML is confirmed by cytogentically identifying the Ph chromosome in the bone marrow; potentially along with other karyotypic abnormalities that may have prognostic significance. Staging (phase) is based on blast percentage in the blood and marrow, degree of basophilia, platelet count, and presence of extramedullary blast proliferation. Patients are diagnosed as chronic phase (CP), accelerated phase or blast phase. Prognosis is largely determined by stage; however, in chronic phase prognostic information is determined by clinical scoring systems (i.e. Sokal, Hasford, and EUTOS). The EUTOS score is based on prognosis with imatinib therapy and is appropriate for this context to

... continued, page 11
pulmonary arterial hypertension. Nilotinib has been associated with arterial pathology. Other practitioners may opt for imatinib and reserve a 2G TKI for salvage. Either approach is reasonable at this time until further information on the prospective management of high risk patients is available.

References

Related to our patient there are concerns over increased arterial disease risk (both peripheral and coronary) potentially mediated or exacerbated by observed elevations in cholesterol and glucose while on nilotinib. We must assess our patient’s risk for arterial disease prior to initiating therapy and obtain baseline cholesterol and glucose levels. If peripheral arterial occlusive disease is confirmed prior to or during therapy, nilotinib should be avoided. Choosing one of the 2G TKIs in our patient requires initial and ongoing cardiopulmonary and cardiovascular evaluations.

High Sokal risk may be an indication for choosing a 2G TKI frontline although this is still an active area of discussion among various international co-operative groups. Given this patient’s disease characteristics close follow-up and molecular monitoring (with quantitative RT-PCR) according to the most recent guidelines is essential. It is clear that the molecular response at 3 months predicts long-term outcomes. CP patients who fail to achieve a BCR-ABL <10% by 3 months have a risk of progression of greater than 10%. What is not known is whether switching to an alternative TKI in patients who fail this milestone will decrease the risk. There is no published prospective data that directly addresses this strategy.

Our practice, despite lack of a formal guideline or expert consensus recommendation, would be to start this patient on a 2G TKI. The choice of agent based upon a thorough assessment of his comorbidities.
Choosing Wisely Canada (CWC) is a campaign to help physicians and patients engage in conversations about unnecessary tests, treatments and procedures and support physician efforts to help patients make smart and effective choices to ensure high quality care.

This past winter we announced that the CHS will be participating in the campaign.

CWC is modeled after the hugely successful Choosing Wisely® campaign in the United States. Initiated and coordinated by the ABIM Foundation, 60 medical societies have to date joined the campaign to develop “Top 5 Lists” of tests and treatments physicians and patients should question – things for which there is strong evidence of overuse, waste, or even harm to patients.

The first eight Canadian medical societies have compiled their lists and they will be presented this April.

ASH presented their list this past December sparking lively debate and interest. We look forward to coming together as a society and developing a Canadian version of this list.

Any questions or comments please contact Chris Hillis (hillisc@mcmaster.ca).

Hicks LK et al. The ASH Choosing Wisely Campaign: Five hematologic tests and treatments to question. Blood 2013 Dec 5; 122:3879.

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**We invite you to attend!**

The Canadian Hematology Society

meets in

Halifax, Nova Scotia

Canada!

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**Please join us, June 13, 2014, Halifax, Nova Scotia!**

This is a joint meeting with
- The Canadian Apheresis Group (CAG), and
- The Canadian Blood and Marrow Transplant Group (CBMTG)

You will not be charged a fee but it is important that you **Please REGISTER**

To register, RSVP by email to: chsincanada@gmail.com
with the following 3 details:
1. Your name
2. Your institution
3. Whether or not you will be joining us for lunch
The Microenvironment will be happy to consider for publication, articles submitted by members who have sponsored student summer projects.

Queries should be directed to:
- Dr. Tom Nevill, The Editor, The Microenvironment
- Email: chs@uniserve.com
The peripheral blood showed a leukoerythroblastic picture with 60% eosinophils and 10% blast cells.

The bone marrow was a dry tap with touch preparation and biopsy showing complete marrow replacement with malignant cells, ranging in appearance from microblasts to large undifferentiated cells, along with prominent eosinophilia.

Lymph node biopsy showed replacement by a similar malignant cell population that were CD45, CD117, CD56, CD5, CD7 and CD38-positive but negative for CD3, TdT and CD123; TcR gene rearrangement was positive. CD3 negativity ruled out T-LBL and CD123 negativity ruled out blastic plasmacytoid dendritic cell neoplasm (“blastic NK cell lymphoma”). Despite the clinical and pathologic features being suspicious for an FGFR1 translocation, karyotype was normal female.

She was treated with Cyclophosphamide and Prednisone; after her hepatic function had improved, Doxorubicin, Vincristine and L-Asparaginase were added. She entered complete remission, had a matched sibling identified and was successfully consolidated with allogeneic stem cell transplantation.
Thrombosis Clinical & Research Fellowships - Up to 3 positions

Applications are encouraged from MDs who have completed or who will complete General Internal Medicine, Respirology and/or Hematology training. Foreign medical graduates with equivalent qualifications are eligible.

Applicants may apply to one of three training streams:

1.) Clinical Fellowship, one-year—To consolidate expertise in thrombosis.
2.) Clinical and Research Fellowship, 2-3 years (to become a clinician investigator in thrombosis (Fellows enroll in the Master’s of Clinical Epidemiology Program at the University of Ottawa).
3.) Clinical and Education Fellowship, 2-3 years (to become a clinician educator in Thrombosis. (Fellows enroll in a Master’s in Education).

To apply, please contact: nlanglois@ohri.ca

Details are also available on the CHS website.

Leukemia/Bone Marrow Transplantation Fellowship Vancouver

The Leukemia/Bone Marrow Transplantation Program of British Columbia offers 1 or 2 Year fellowships to provide advanced training in the management of adults with hematological malignancies including all aspects of allogeneic and autologous hematopoietic stem cell transplantation (HSCT).

Candidates should be registered in, or completed a recognized hematology or oncology training program.

For more information: leukemiabmtprogram.org

Interested candidates should submit a CV and names of three references to:

Dr. Donna Forrest, Fellowship Director,
Leukemia/BMT Program
BC Cancer Agency & Vancouver General Hospital

Phone: (604) 875-4089
FAX: (604) 875-4763
Email: dforrest@bccancer.bc.ca
Membership Matters

The Canadian Hematology Society has represented all physicians and scientists with an interest in the discipline in Canada since it was founded in 1971, and currently has over 400 members.

Active Membership
- Physicians in the practice of clinical or laboratory hematology in Canada
- Scientists with PhD degrees making continuing contributions to research related to hematology in Canada
- Allied Health Professionals with university degrees making sustained contributions to clinical or laboratory hematology practice or hematology research in Canada.

Only active members shall:
- vote
- hold office
- receive CHS grants, and
- pay dues.

Associate Members
- Residents and fellows engaged in hematology training
- Masters and PhD graduate students
- Post-doctoral fellows engaged in hematology research

Associate members will not be required to pay dues until completion of their training.

Emeritus Members
- All individuals who have retired from full time hematology practice or research, or those who were active members and request a transfer of status with adequate reason.

Honorary Membership
- Non-members may be invited to become Honorary Members of the corporation by virtue of their outstanding contributions to any discipline which is of importance to hematology.

CHS members are reminded ... that dues for the year 2014, were due on January 1, 2014.

Your $75. annual dues payment may be made online at the CHS website: www.canadianhematologysociety.org

Or by mail to: Canadian Hematology Society, 199-435 St. Laurent Blvd., Ottawa, Ontario K1K 2Z8

Please provide the following information with your payment:

2013 Membership Renewal: Canadian Hematology Society

Membership Status
Active □
Associate □
Emeritus □

Has your status changed?
Yes □
No □

Name: ______________________________
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Work Address: __________________________

Work Phone: __________________________
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